

An exploratory study of sunitinib plus paclitaxel as first-line treatment for patients with advanced breast cancer

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Background: Sunitinib has shown single-agent activity in patients with previously treated metastatic breast cancer (MBC). We investigated the safety of the combination of sunitinib and paclitaxel in an exploratory study of patients with locally advanced or MBC.

Methods: Patients received oral sunitinib 25 mg/day (with escalation to 37.5 mg/day as tolerated) on a continuous daily dosing schedule and paclitaxel 90 mg/m² on days 1, 8, and 15 of each 28-day cycle. Study endpoints included safety (primary endpoint), pharmacokinetics, and antitumor activity.

Results: Twenty-two patients were enrolled. The most frequent adverse events (AEs) were fatigue/asthenia (77%), dysgeusia (68%), and diarrhea (64%). Grade 3 AEs included neutropenia (43%), fatigue/asthenia (27%), neuropathy (18%), and diarrhea (14%). No drug–drug interaction was observed on the basis of pharmacokinetic analysis. Of 18 patients with measurable disease at baseline, 7 (38.9%) achieved objective responses (including 2 complete and 5 partial responses). Clinical responses were observed in three of nine patients with triple-negative receptor status (estrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor-2 negative).

Conclusions: These data indicate that sunitinib and paclitaxel in combination are well tolerated in patients with locally advanced or MBC. No drug–drug interaction was detected and there was preliminary evidence of antitumor activity.

Key words: breast cancer, paclitaxel, sunitinib, tyrosine kinase inhibitor

introduction

The contribution of angiogenesis to tumor development is a subject of increasing importance to oncology. Tumor-associated angiogenesis is in part controlled by signaling through the vascular endothelial growth factor (VEGF) and platelet-derived growth factor pathways. Activation of both of these pathways is required for the development and growth of all solid tumors, including breast cancer, and both play an important role in the formation of metastases. Studies have shown that vascular endothelial growth factor receptors (VEGFRs) are often overexpressed in breast cancer [1, 2], and that high levels of VEGF are predictive of poor survival and poor response to treatment in advanced breast cancer [3]. Similarly, the overexpression of platelet-derived growth factor receptors (PDGFRs) is common in breast cancer tumors and

may predict shortened survival and treatment failure in patients with advanced disease [4].

As a direct consequence of the identification of antiangiogenic targets such as VEGFR and PDGFR, novel agents have been developed that inhibit these signaling pathways. Preclinical data from studies using targeted agents have provided a viable justification for their development in the clinic [5]. Several clinical studies of targeted agents have been conducted in patients with breast cancer and have shown early evidence of clinical activity [6, 7]. In addition, three phase III clinical trials with the anti-VEGF antibody bevacizumab, given in combination with taxane therapy, have demonstrated that progression-free survival in the combination was superior to taxane alone in the first-line treatment of metastatic breast cancer (MBC) [8–10]. These data provide proof of concept for the activity of anti-VEGF agents in the treatment of breast cancer, and it has been suggested that dual inhibition of both VEGFR and PDGFR may prove more effective than inhibition of either target alone [11].

Sunitinib is an oral, multitargeted tyrosine kinase inhibitor of VEGFR-1, -2, and -3, PDGFR- α and - β , stem-cell factor receptor

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(KIT), FMS-like tyrosine kinase 3 (FLT 3), colony-stimulating factor 1 receptor (CSF-1R), and glial cell line-derived neurotrophic factor receptor (RET) [12–17]. Sunitinib has inhibited tumor growth in breast cancer models [12, 15, 18] and preliminary evidence of single-agent activity was reported in a phase II study of sunitinib in heavily pretreated patients with MBC [objective response rate (ORR) 11%] [19]. When given with chemotherapy, a reduction in the rate of tumor growth of human breast cancer xenografts was observed in mice and a survival benefit reported [12, 20]. As such, it has been hypothesized that sunitinib will have superior clinical activity in breast cancer when administered in combination with other anticancer treatments.

Here, we present data from an exploratory study of sunitinib given in combination with paclitaxel to patients with locally advanced or MBC. The study aimed to analyze the pharmacokinetic profiles of sunitinib and paclitaxel when given in combination and to assess the tolerability and preliminary antitumor activity of the combination.

methods

study population

Female patients, aged ≥ 18 years, with unresectable breast cancer that was locally recurrent or metastatic and not amenable to curative resection or radiation with curative intent were recruited. All acute toxic effects of prior therapy or surgical procedures were to be resolved to grade one or less (except alopecia). Other inclusion criteria included adequate organ function, as defined by hematology and blood chemistry, Eastern Cooperative Oncology Group performance status of one or less, and the provision of informed consent.

Exclusion criteria included prior chemotherapy for advanced disease (hormonal therapy in the adjuvant and/or advanced disease setting was allowed), prior adjuvant taxane therapy with relapse ≤ 12 months from the last dose, and prior treatment with tyrosine kinase inhibitors, VEGF inhibitors, or other inhibitors of angiogenesis, including sunitinib. Patients with human epidermal growth factor receptor-2 (HER2)-positive disease were excluded unless the patient had previously received trastuzumab.

Major surgery, radiotherapy, or systemic therapy within 3 weeks of the start of treatment was not allowed, with the exception of palliative radiotherapy to nontarget metastatic lesions. Comorbid conditions that constituted exclusion from the study included uncontrolled hypertension ($>150/100$ mmHg) or brain metastases, diagnosis of any second malignancy within the last 3 years, cardiac conditions, and transient ischemic attack or pulmonary embolus in the 12 months before study entry.

study design

This was an exploratory, nonrandomized study evaluating sunitinib [oral continuous daily dosing (CDD) schedule] combined with paclitaxel (i.v. weekly for 3 weeks then 1 week off treatment) in patients with locally recurrent or MBC. Both drugs were administered in 4-week cycles for up to 1 year.

The primary endpoint was safety and toxicity. Secondary endpoints included pharmacokinetic parameters of paclitaxel and sunitinib (and its active metabolite SU12662), alone and coadministered and antitumor activity of the paclitaxel and sunitinib combination.

The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable local regulatory requirements and laws. The institutional review board or independent ethics committee of each participating center approved the study protocol, and all patients provided informed consent.

study treatments

Treatment was administered in 4-week cycles. Sunitinib 25 mg was administered orally, once daily, on a CDD schedule. Patients completing one cycle of treatment with minimal adverse effects could escalate their dose of sunitinib to 37.5 mg/day in subsequent cycles. Patients experiencing dose-limiting toxic effects (DLTs; defined as a grade 4 hematologic toxicity, grade 3 non-hematologic toxicity excluding uncontrollable nausea or vomiting, or need for dose modification) attributable to sunitinib were permitted to have 1-week off-treatment periods, as required, to manage toxicity. Patients with recurrent grade 3 or 4 adverse events (AEs) other than neutropenia could receive a reduced dose of sunitinib (12.5 mg/day).

Paclitaxel was administered i.v. as a 1-h infusion weekly for 3 weeks followed by 1 week off treatment, at a starting dose of 90 mg/m²/week. The paclitaxel dose could be reduced to 65 mg/m² in subsequent cycles on the basis of tolerability. One dose could be missed in the case of grade 3 toxicity. Paclitaxel could be discontinued at the discretion of the investigator. Patients discontinuing one agent due to maximum benefit or unacceptable toxicity could continue single-agent therapy with the remaining agent. Patients were pretreated with standard medications before paclitaxel infusion. Hematopoietic growth factors (granulocyte colony-stimulating factor) were permitted after cycle 1 to maintain neutrophil counts $>1500/\mu\text{L}$.

assessments

Pharmacokinetic parameters for paclitaxel, sunitinib, SU12662, and total drug (sunitinib + SU12662) were estimated when drugs were administered alone and in combination.

Physical examination, cardiac function, and blood chemistry were reassessed once per cycle. Hematology was assessed before each paclitaxel dose. AEs were graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events, version 3.0. Follow-up assessments were carried out 28 days after the last dose of study medication.

Tumor assessments were conducted every 8 weeks and evaluated according to RECIST [21]. Objective responses included both complete responses (CRs) and partial responses (PRs) that were confirmed at least 4 weeks after the response was initially documented. Patients with evaluable/measurable disease at baseline were included in these analyses.

statistical methods

The sample size of 22 patients was determined on an empirical basis, based upon prior experience with small sample sizes in phase I studies [22, 23]. This sample size was felt to be adequate to characterize the safety of treatment for investigation in future trials. Descriptive statistics were used to summarize patient characteristics, compliance, efficacy, safety, and pharmacokinetic parameters.

Pharmacokinetic parameters were calculated by noncompartmental analysis of concentration–time data using WinNonlin version 4.1.a. For paired observations, dose corrections for maximum concentration (C_{max}), area under the curve (AUC), and plasma concentrations to the intended dose were made.

results

patient population and disposition

Twenty-two patients were enrolled in the study; baseline characteristics are shown in Table 1. All 22 patients were included in the safety and pharmacokinetic analyses and all 22 received at least one dose of paclitaxel; 21 patients received at least one dose of sunitinib. Eighteen patients (82%) discontinued treatment. Of these, one discontinued following the investigator's assessment that the maximum benefit from

paclitaxel had been achieved and another discontinued as response was such that further resection of the lesion was possible. Thirteen patients (59%) discontinued due to disease progression: 1 patient due to an AE (chronic leg ulcer), 1 due to withdrawal of consent, and 1 due to failure to meet eligibility criteria (preexisting hyponatremia discovered before the first dose of sunitinib). Four patients (18%) completed 1 year of study treatment.

treatment summary

Patients received a median of six cycles of sunitinib (range 2–15) and five cycles of paclitaxel (range 1–14). The dose of sunitinib was escalated to 37.5 mg in 14 of 21 (67%) patients and was maintained at 25 mg or reduced to 12.5 mg in 7 of 21 (33%) patients. The dose of paclitaxel was reduced to 65 mg/m² in 8 of 22 (36%) patients. At least one dose delay of sunitinib and of paclitaxel was experienced by 13 of 22 (59%) patients.

Table 1. Patient baseline characteristics

Patient characteristics	Patients (N = 22)
Age, years	
Mean (SD)	58.1 (9.7)
Range	37–74
Gender, n (%)	
Female	22 (100)
Race, n (%)	
White	17 (77)
Black	5 (23)
Extent of disease, n (%)	
Locally recurrent	2 (9)
Metastatic	20 (91)
Histology, n (%)	
Ductal	17 (77)
Ductal + lobular	1 (4.5)
Lobular	3 (14)
Inflammatory	1 (4.5)
Receptor status, n (%)	
ER (positive/negative)	13/9 (59/41)
PgR (positive/negative/unknown)	9/12/1 (41/55/4.5)
HER2 (positive/negative/unknown) ^a	1/20/1 (5/91/4.5)
Triple negative ^b	9 (40.9)
Prior adjuvant chemotherapy (%)	63.6
Disease, n (%)	
Measurable	18 (82)
Nonmeasurable	4 (18)
Location of disease, n (%)	
Lymph node	12 (55)
Liver	8 (36)
Lung	7 (32)
Bone	13 (59)
ECOG performance status, n (%)	
0	12 (55)
1	10 (45)

^aHER2 measured by IHC3+ or FISH+.

^bHER2 negative, ER negative, and PgR negative.

SD, standard deviation; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor-2; ECOG, Eastern Cooperative Oncology Group.

safety

Adverse events are presented in Tables 2 and 3. The most frequent non-hematologic AEs of any grade were fatigue/asthenia (77%), dysgeusia (68%), and diarrhea (64%). Four patients (18%) experienced grade 2 or 3 hypertension. Other grade 3 non-hematologic events included fatigue/asthenia (27%), neuropathy (18%), and diarrhea (14%). There was one case of grade 4 pulmonary embolism and one case of grade 1 vaginal hemorrhage that were considered related to study treatment. One DLT occurred (neutropenia), resulting in a temporary reduction in the paclitaxel dose. No deaths occurred on study.

Transient neutropenia was the most common hematologic toxicity, occurring at grade 3/4 in 48% of patients. Neutrophil counts routinely rebounded during treatment on the sunitinib CDD schedule. No cases of neutropenic fever or infection were reported.

pharmacokinetics

Plasma pharmacokinetic parameters and geometric mean ratios for patients with paired observations for sunitinib and paclitaxel following multiple dosing with sunitinib alone (25 or 37.5 mg) and with paclitaxel (90 mg/m²) are summarized in Table 4.

Geometric mean ratios of C_{max} and AUC₂₄ (area under the plasma concentration–time curve from time 0 to 24 h after dose) for sunitinib and C_{max}, AUC_{last} (AUC from time zero to time of the last measurable concentration), and AUC_∞ (area under the plasma concentration–time curve from time zero to infinity) for paclitaxel did not indicate clinically significant changes in pharmacokinetic parameters when sunitinib or paclitaxel were administered alone or in combination.

efficacy

Of 18 patients with measurable disease at baseline, two CRs (11.1%) and five PRs (27.8%) were reported, resulting in an overall ORR of 38.9%. Stable disease ≥6 months was observed in five patients, three of whom had nonmeasurable disease (two patients with bone only disease and one with bone lesions plus pleural effusion). Responses were recorded in three of nine patients with triple-negative [estrogen receptor (ER) negative, progesterone receptor (PgR) negative, and HER2 negative] receptor status. Median progression-free survival was 33 weeks [15.6–not reached (NR)]. Median overall survival was 66.6 weeks (58.4–NR), with a 1-year survival rate of 84% (range 70%–100%).

discussion

Data from this exploratory study indicate that sunitinib given in combination with paclitaxel has an acceptable safety profile in patients with advanced breast cancer. No pharmacokinetic drug–drug interaction was observed between paclitaxel and sunitinib. The data also indicate that the combination has clinical activity in this patient population.

The safety profile of the combination of sunitinib and paclitaxel is similar to that of each agent given as monotherapy [9, 19], as demonstrated by a lack of unexpected AEs. Most AEs were mild to moderate and easily

Table 2. Non-hematologic adverse events reported by at least 15% of patients regardless of relationship to treatment

Adverse event ^a	Sunitinib and paclitaxel (N = 22)				Total, n (%)
	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	
Fatigue/asthenia	4 (18)	7 (32)	6 (27)	0	17 (77)
Dysgeusia	8 (36)	6 (27)	1 (4.5)	0	15 (68)
Diarrhea	6 (27)	5 (23)	3 (14)	0	14 (64)
Alopecia	8 (36)	5 (23)	0	0	13 (59)
Nausea	5 (23)	6 (27)	1 (4.5)	0	12 (55)
Vomiting	8 (36)	2 (9.1)	1 (4.5)	0	11 (50)
Rash	4 (18)	6 (27)	0	0	10 (45)
Neuropathy (peripheral and peripheral sensory neuropathy)	1 (4.5)	4 (18.2)	4 (18.2)	0	9 (41)
Dyspepsia	3 (14)	4 (18)	2 (9.1)	0	9 (41)
Stomatitis	4 (18)	4 (18)	0	0	8 (36)
Anorexia	1 (4.5)	4 (18)	1 (4.5)	0	6 (27)
Hand-foot syndrome	2 (9.1)	2 (9.1)	2 (9.1)	0	6 (27)
Cough	4 (18)	2 (9.1)	0	0	6 (27)
Dyspnea	2 (9.1)	2 (9.1)	2 (9.1)	0	6 (27)
Mucosal inflammation	3 (14)	3 (14)	0	0	6 (27)
Insomnia	5 (23)	0	0	0	5 (23)
Epistaxis	3 (14)	1 (4.5)	1 (4.5)	0	5 (23)
Anxiety	3 (14)	1 (4.5)	0	0	4 (18)
Depression	3 (14)	1 (4.5)	0	0	4 (18)
Dizziness	2 (9.1)	1 (4.5)	1 (4.5)	0	4 (18)
Headache	4 (18)	0	0	0	4 (18)
Edema peripheral	2 (9.1)	1 (4.5)	1 (4.5)	0	4 (18)
Pruritus	4 (18)	0	0	0	4 (18)
Skin discoloration	4 (18)	0	0	0	4 (18)
Hypertension	0	2 (9.1)	2 (9.1)	0	4 (18)

^aNational Cancer Institute—Common Terminology Criteria for Adverse Events version 3.0.

Table 3. Hematologic adverse events (laboratory abnormalities: worst grade by patient)

	Sunitinib and paclitaxel (N = 21 ^a)				Total, n (%)
	Grade 1 ^b , n (%)	Grade 2 ^b , n (%)	Grade 3 ^b , n (%)	Grade 4 ^b , n (%)	
Neutrophils ^c	5 (24)	5 (24)	9 (43)	1 (4.8)	20 (95)
White blood cells	3 (14)	6 (29)	10 (48)	0	19 (91)
Lymphocytes	2 (9.5)	3 (14)	7 (33)	3 (14)	15 (71)
Hemoglobin	8 (38)	9 (43)	2 (10)	0	19 (91)
Platelets	7 (33)	0	0	0	7 (33)

^aOne patient received treatment with paclitaxel only on study and was withdrawn due to ineligibility (G3 hyponatremia) before administration of sunitinib. No hematologic data were collected.

^bNational Cancer Institute—Common Terminology Criteria for Adverse Events version 3.0.

^cNo cases of neutropenic infection or fever were reported.

managed. The most frequently reported non-hematologic AEs included fatigue, dysgeusia, and diarrhea, and the most common grade 3 non-hematologic AEs were fatigue, neuropathy, and diarrhea. Neuropathy is a known side-effect of paclitaxel treatment; an incidence of 17%–21.6% has previously been reported with paclitaxel monotherapy [9, 24], similar to the rate observed in this study with the sunitinib and paclitaxel combination (18%).

A significant level of hypertension may have been expected following treatment that includes an anti-VEGF agent. In the current trial, two patients (9%) experienced grade 3

hypertension. Hypertension, as well as bleeding and thrombotic events, has previously been reported with the anti-VEGF agent bevacizumab when combined with paclitaxel; grade 3 hypertension was reported in 53 of 365 (14.5%) patients who received bevacizumab plus paclitaxel in the phase III registration trial, while grade 3 thrombosis or embolism occurred at an incidence of 1.6% and hemorrhage at 0.5% [9]. No severe (grade 3 or 4) bleeding events were reported in the current study, although there was one occurrence of grade 1 vaginal hemorrhage. Bleeding events in the current study appeared to be somewhat increased compared with these

Table 4. Summary of sunitinib and paclitaxel pharmacokinetic parameters following administration of sunitinib alone or in combination with paclitaxel

Dose (sunitinib/paclitaxel)/ analyte parameter	Sunitinib or paclitaxel alone mean (CV%), median	Sunitinib + paclitaxel, mean (CV%), median	Geometric mean ratio (90% CI)
25 mg/90 mg/m ² , <i>n</i> = 16 ^a			
Sunitinib	Cycle 1 day 22	Cycle 1 day 15	Cycle 1 day 15/cycle 1 day 22
C _{max} (ng/ml)	46.5 (40), 44.7	49.8 (40), 48.4	1.06 (0.81–1.40)
AUC ₂₄ (ng·h/ml)	943 (42), 904	979 (41), 956	1.03 (0.78–1.36)
Paclitaxel	Cycle 1 day 1	Cycle 1 day 15	Cycle 1 day 15/cycle 1 day 1
C _{max} (ng/ml)	4080 (58), 3990	4910 (36), 5725	1.29 (0.92–1.81)
AUC _∞ (ng·h/ml)	6450 (26), 6289	7964 (24), 8180	1.24 (1.05–1.46)
<i>t</i> _{1/2} (h)	9.9 (34), 9.6	13.2 (35), 13.6	NA
CL (l/h)	27.3 (33), 24.7	22.0 (30), 20.0	0.81 (0.67–0.97)
37.5 mg/90 mg/m ² , <i>n</i> = 8			
Sunitinib	Cycle 2 day 22 ^b	Cycle 2 day 15 ^b	Cycle 2 day 15/cycle 2 day 22
DC-C _{max} (ng/ml)	48.1 (42), 50.9	52.7 (45), 58.1	1.03 (0.64–1.67)
DC-AUC ₂₄ (ng·h/ml)	976 (43), 1009	972 (45), 991	0.97 (0.59–1.57)
Paclitaxel	Cycle 1 day 1 ^b	Cycle 2 day 15 ^b	Cycle 2 day 15/cycle 1 day 1
C _{max} (ng/ml)	3852 (41), 4570	4975 (51), 3752	1.29 (0.85–1.95)
AUC _∞ (ng·h/ml)	7766 (68), 5783	8737 (46), 6880	1.20 (0.82–1.74)
<i>t</i> _{1/2} (h)	9.7 (29), 9.6	12.6 (20), 12.5	NA
CL (l/h)	26.6 (50), 25.1	20.9 (35), 20.8	0.83 (0.56–1.23)

^aPaired observations.

^bIn three of eight patients, paclitaxel dose was reduced to 65 mg/m² on cycle 2 day 15. For these patients, dose correction for C_{max}, AUCs, and plasma concentration to the intended dose was made.

CV, coefficient of variation; CI, confidence interval; C_{max}, maximum concentration; AUC₂₄, area under the plasma concentration–time curve from time 0 to 24 h after dose; AUC_∞, area under the plasma concentration–time curve from time zero to infinity; *t*_{1/2}, terminal elimination half-life; NA, not applicable; CL, total clearance; DC-C_{max}, dose-corrected (i.e. reference dose: 25 mg) maximum concentration; DC-AUC₂₄, dose-corrected (i.e. reference dose: 25 mg) area under the plasma concentration–time curve from time 0 to 24 h after dose.

historical data. Epistaxis of any grade occurred in five (23%) patients (grade 3 in one patient) and there was one occurrence of treatment-related grade 1 vaginal hemorrhage. There was one treatment-related thrombotic event reported (grade 4 pulmonary embolism).

The most commonly reported grade 3/4 hematologic AE was neutropenia, occurring in 10 patients (47.8%). Growth factor support to maintain dose intensity was administered to 16 patients (73%). Grade 3/4 neutropenia has previously been reported at an incidence of 0.3%–11.5% with paclitaxel monotherapy [9, 24]. Growth factor support was not permitted during cycle 1 which allowed baseline levels of treatment-related neutropenia to be determined. As sunitinib has inherent myelosuppressive properties, the combined myelosuppressive effects of both agents may explain the increased rate of neutropenia in this study, compared with studies of single-agent paclitaxel.

While the majority of patients experienced at least one dose interruption due to AEs, only one of the 21 patients who received sunitinib and paclitaxel discontinued treatment due to an AE. This indicates that with growth factor support and intermittent periods off treatment, the regimen is well tolerated with few patients discontinuing due to toxicity. These data are consistent with those recently reported from an exploratory study in which sunitinib was administered with docetaxel [22] and indicate that these drugs can be safely coadministered at standard doses in the treatment of advanced breast cancer.

While cross-trial comparisons are always limited, the antitumor ORR of 38.9% observed in the current study following addition of sunitinib to paclitaxel is similar to that observed in a phase III, open-label, randomized trial of bevacizumab plus paclitaxel for the first-line treatment of MBC (36.9%) [9]. However, median overall survival in the current study was 66.6 weeks (~16 months), and lower than observed with the combination of bevacizumab plus paclitaxel (26.7 months) [9].

Clinical responses were observed in three of nine (33.3%) patients with the triple-negative receptor phenotype (ER–, PgR–, and HER2–). Activity against triple-negative breast cancer was also reported following treatment with sunitinib monotherapy in a phase II study of heavily pretreated patients with MBC who demonstrated a 15% response rate (3 of 20 patients) [19]. The activity of sunitinib in triple-negative breast cancer is being further evaluated by testing sunitinib versus standard of care in a phase II study (SUN 1077) of previously treated patients.

In conclusion, the results of this study demonstrate that sunitinib administered in combination with paclitaxel to patients with advanced breast cancer is well tolerated without any drug–drug interaction. Sunitinib continues to be evaluated as a potential treatment of advanced breast cancer in combination with chemotherapy and studies with sunitinib are continuing in the neoadjuvant breast cancer setting. In January 2009, accrual completed to the phase III SUN 1064 study examining the combination of sunitinib and docetaxel versus

docetaxel alone as first-line treatment of patients with advanced breast cancer. In addition, enrollment to SUN 1099 completed in February 2009. This is a phase III, second-line study of sunitinib plus capecitabine versus capecitabine alone in patients with advanced breast cancer. However, a phase III combination study of sunitinib plus paclitaxel versus bevacizumab plus paclitaxel (SUN 1094) was stopped in 2009 as interim analyses showed the primary end point could not be met.

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disclosure

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